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Original article

Treatment of a patent ductus arteriosus in premature infants

Summary

Background. Patent ductus arteriosus in premature infants is often treated because of its effect on pulmonary disease and the later development of bronchopulmonary dysplasia. This view has now been challenged.

Materials and methods. Relevant publications have been selected from review articles in international journals, mainly through searches in the PubMed and Cochrane databases.

Results. Recent research indicates that a persistent ductus arteriosus should be considered physiological in small premature infants, serving as a useful shunt allowing blood to flow from right to left during the first postnatal days when pulmonary arterial pressure is high, and from left to right in cases where significant pulmonary disease is present and increased pulmonary blood flow would improve oxygenation. A patent ductus arteriosus does not exacerbate acute pulmonary disease or increase the risk of bronchopulmonary dysplasia, intraventricular haemorrhage, necrotising enterocolitis or other complications in survivors.

Interpretation. Treatment of a patent ductus arteriosus with COX inhibitors like indomethacin and ibuprofen increases the risk of bronchopulmonary dysplasia without reducing other complications or preventing death. A large patent ductus arteriosus has significant haemodynamic effects and should be treated with fluid restriction, diuretics and inotropic drugs before closure is considered. Surgical closure of a patent ductus arteriosus has been linked to neurosensory impairment in survivors.

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In foetal life, the ductus arteriosus connects the pulmonary artery to the aorta. At birth the ductus contracts and is functionally closed within a few days. Closure of the ductus is a result of several mechanisms, the most important being the increase in blood oxygen tension at birth and reduction in blood levels of the prostaglandins PGE1, PGE2 and PGI1 (1). Usually the ductus obliterates permanently within a few months but it may stay open for up to a year after birth.

In infants born prematurely ductal closure is often delayed compared to infants born at term. This condition is called patent ductus arteriosus (PDA). Delayed closure is partly due to immaturity of ductal wall musculature and partly to clinical conditions which prevent the normal rise in arterial oxygen concentration at birth. The incidence of PDA is therefore inversely related to gestational age and is seen more often in infants with respiratory distress syndrome or other diseases resulting in problems with adequate oxygenation after birth. Other conditions such as phototherapy for hyperbilirubinaemia and overhydration during the first few days of life have also been associated with PDA (2). In infants with a birth weight of less than 1 000 grams, the incidence of PDA is approximately 50 %.

In recent years there has been a significant change in views regarding the clinical significance of a PDA. From being a condition considered a severe complication to prematurity, PDA is now considered by many experts to be a partly physiological condition which rarely needs treatment. This view is supported by many recent studies indicating that the side effects and results of treatment might be more harmful to the infant than the PDA itself (3–6). This review article discusses the studies behind this shift in paradigm.

Materials and methods

This is a non-systematic review. Relevant publications in international journals with peer review have mainly been identified through searching in the PubMed and Cochrane databases.

Pathophysiological significance of PDA

In foetal life the ductus shunts blood from the pulmonary artery (right) to the aorta (left) because of the high vascular resistance in the lungs. After birth the bloodstream in a PDA will be from left (aorta) to right (pulmonary artery), since the vascular resistance is higher in the systemic than in the pulmonary circulation. In newborns, however, vascular resistance in the lungs continues to be quite high for the first postnatal days, and is often comparable to vascular resistance in the systemic circulation (7). A bidirectional shunt in the ductus is therefore common during the first few days of life. This might result in reduced arterial oxygenation during episodes of crying and unrest in otherwise healthy newborns. The left-to-right shunt in a PDA will first become clinically significant when pulmonary vascular resistance has been considerably reduced. In term infants this might take several weeks.

Clinical presentation of PDA

In premature infants, the haemodynamic consequences of a PDA can usually be seen already a few days after birth. This is mainly attributable to a more rapid fall in pulmonary vascular resistance in premature than in term infants. Furthermore, premature infants have less developed compensatory mechanisms as they are less able to increase sys-

Main message

- A patent ductus arteriosus does not exacerbate lung disease and does not increase the incidence of other complications of prematurity.
- Prophylactic or early treatment of a patent ductus arteriosus seems to be more harmful than the consequences of the PDA as such.
- Surgical closure of a patent ductus arteriosus in a small premature infant is associated with neurosensory impairment.

temic cardiac output by increasing stroke volume and heart rate. This capability is even more reduced in sick infants, such as infants with significant lung disease (8). Left heart cardiac failure with dilation of the left atrium and ventricle and pulmonary congestion is therefore seen earlier in premature infants.

The presence of a PDA has been seen as one of the most important risk factors for a number of complications to prematurity. If an infant with a PDA is not able to increase cardiac output to compensate for the blood shunted across the ductus, reversed flow might be seen in the aorta (ductal steal). This will result in reduced blood flow to several organs including the brain, kidney and intestines (9, 10). The presence of a PDA has therefore been seen as a cause of brain damage (both intraventricular haemorrhage and periventricular leukomalacia) resulting in cerebral palsy, necrotising enterocolitis and increased mortality. More specifically, a PDA has been related to an increased need for mechanical ventilation and thus identified as a major risk factor for development of bronchopulmonary dysplasia (BPD).

It is difficult to evaluate the haemodynamic significance of a PDA only from clinical variables such as the character of the heart murmur, pulse pressure, blood pressure and other clinical signs. In most cases, treatment indications are therefore considered from an evaluation of clinical signs together with echocardiographic and radiological findings.

Effects of PDA on lung function

A haemodynamically significant PDA is often associated with deterioration of an infant's clinical situation, such as an increased need for oxygen supplementation and ventilator support. However, it has been shown that this effect on the infant is related more to the infant's ability to compensate for the left-to-right shunt by increasing cardiac output than to the actual shunt size (8). The clinical picture of a very sick infant can therefore be considerably worsened by a relatively small shunt, while a large shunt in an otherwise healthy infant need not have any effect other that those related to an increase in cardiac output.

These clinical studies are also supported by experimental studies on newborn lambs (10). By preparing the duct with formaldehyde it was possible to establish a PDA and vary the shunt size. It was found that although blood flow to the lungs increased with shunt size, this was not associated with any changes in ventilator parameters such as compliance or resistance.

There are, however, few clinical studies published on the effect of a PDA on lung mechanics, and most studies have related to therapeutic closure of the duct (12–15). Most studies find no or small changes in lung mechanics after closure of a PDA. The observed worsening of the clinical situation of infants with a PDA is therefore probably due more to effects on the systemic circulation than to pulmonary effects. A PDA may also influence gas exchange in the lungs by reducing gas diffusion, changes which will not result in altered lung mechanics.

Cardiovascular effects of PDA

The most important effects of a PDA are those related to the systemic circulation. Animal studies have shown an increase in systolic and decrease in diastolic blood pressure as well as an increase in stroke volume and minute volume with increasing shunts (10), similar to what is found in echocardiographic studies of premature infants (8). With large shunts, aortic diastolic blood flow will be significantly reduced and also reversed if cardiac output can no longer compensate for shunt blood volume. It is therefore relevant to measure cardiac output in infants with a PDA. However, it is found to be very difficult to measure blood flow at the aortic valve or in the aorta routinely by means of echocardiography in a clinical setting, and cardiac output is therefore rarely measured in infants with a PDA. However, it has been shown that blood flow in the superior vena cava is a good substitute for cardiac output and also easier to measure (16, 17). The results of such measurements should probably be a major variable in the evaluation of treatment indications for PDA.

Treatment of premature infants with PDA

Until recently a PDA has been regarded as a condition needing as early and effective treatment as possible. Prophylactic treatment of PDA has also been recommended for the most premature and sickest infants (18). Treatment is either surgical closure by means of a left-side thoracotomy or pharmacological, using COX inhibitors such as indomethacin or ibuprofen (19). Meta-analyses have shown that there are no significant differences in successful ductal closure using indomethacin or ibuprofen (20), long or short treatment courses (21) or surgical or pharmacological treatment with regard to the final outcome for the infant (19). Furthermore, side effects do not seem to differ significantly for the various treatment strategies, except that surgical closure rarely affects kidney function, whereas this is commonly seen in infants treated with COX inhibitors, particularly indomethacin.

Few studies have documented the native course of a PDA in premature infants. A study from 1978 followed premature infants with a birthweight of ≤ 1 500 grams and respiratory distress syndrome who developed heart failure because of a PDA (22).

Table 1. Frequencies of patent ductus arteriosus (PDA) in premature infants with gestational age 22–30 weeks. Mortality and bronchopulmonary dysplasia (BPD) frequencies are shown for infants with and without PDA as well as for different treatment strategies (only indomethacin, only surgery, indomethacin followed by surgery, or fluid restriction only). Infants who died within the first two postnatal days and infants who did not need mechanical ventilation at 24 hours postnatal age are not included. Data extracted from the Norwegian Extreme Prematurity Study (23).

	GA	Patients	Died (%)	BPD (%)	Died/BPD (%)
Whole cohort	22–30	272	36 (13.2)	130 (47.8)	158 (58.1)
Treated for PDA					
Only indomethacin	24–29	24			
Only surgery	22–27	30			
Indomethacin and surgery	23–27	10			
Total		64	5 (7.8)	44 (68.8)[1]	46 (71.9)[1,2]
Only fluid restriction	23–29	18	4 (22.2)	10 (55.6)	12 (66.7)
Not treated for PDA[3]	22–30	178	26 (14.6)	72 (40.4)	96 (53.9)
Asymptomatic PDA	24–28	37	5 (13.5)	12 (32.4)	17 (45.9)
No signs or symptoms of PDA	22–30	141	21 (14.9)	60 (42.6)	79 (56.0)

[1] $p < 0.01$ vs infants not treated for PDA
[2] Three infants who died also had BPD
[3] Data not available for 12 infants

These infants were treated pharmacologically for heart failure and the ductus finally closed in most of them. Infants with a PDA needed mechanical ventilation significantly longer than infants without a PDA and also had a slightly but not significantly higher mortality.

Table 1 shows the incidence of and treatment of PDA in a cohort of extremely small premature infants, data taken from the Norwegian Extreme Prematurity Study (23). The mortality and incidence of BPD is shown in relation to the different treatment strategies. As shown, surgical closure of PDA was more common in the most premature infants, 15/17 infants with a gestational age of < 24 weeks had their PDA surgically ligated. Furthermore, BPD was more common in infants treated for PDA than in untreated infants and in infants without PDA. However, BPD was also equally common in infants without a diagnosis of PDA as in infants with an asymptomatic PDA.

Recent views on PDA

Most studies of the clinical significance of PDA have failed to show any significant relationship between the presence of and treatment for a PDA and final outcome in terms of mortality and morbidity. Even prophylactic (within 24 hours of birth) surgical closure of PDA in infants with birth weight < 1 000 grams showed no differences in mortality, BPD, retinopathy of prematurity or intraventricular haemorrhage compared to infants who had their PDA ligated when a haemodynamically significant PDA was diagnosed later (24). Nor did a study comparing prophylactic treatment with indomethacin to placebo at 12 hours find any significant difference in the duration of oxygen supplementation or mechanical ventilation, BPD, septicaemia, necrotising enterocolitis, retinopathy of prematurity or mortality, although infants who were given indomethacin had a significantly lower incidence of PDA (25). However, treated infants had significantly less intraventricular hemorrhage. It has since been shown that this is due to the direct effect of indomethacin on cerebral vasculature, and is not related to ductal closure (26).

It is particularly the results of the large TIPP study (Trial of Indomethacin Prophylaxis in Preterm Infants) which have almost resulted in a paradigm shift in the view on the significance of a PDA in premature infants (27–29). Many now believe that the presence of a PDA has a very modest pathophysiological impact on the premature infant, and treatment should therefore be indicated for very few infants (3–6). It is now emphasized that a PDA in a premature infant is a physiological condition which allows shunting between the left and the right circulation, from right to left during the first few postnatal days when pulmonary vascular resistance is high, and from left to right in cases of severe lung disease when an increase in pulmonary blood flow could be beneficial. In two commentary articles in the Journal of Pediatrics it is emphasized that the consequences of treatment for PDA (pharmacological side effects and surgery) might be more harmful to the infant than the presence of a PDA itself (5, 6). In the following the studies leading to this shift in paradigm will be discussed.

In the first report from the TIPP study it was found that prophylactic treatment of a PDA had no effect on mortality or neurosensory development at 18 months of age, although the presence of PDA was reduced by more than 50 % (24 % versus 50 %) in treated infants compared to controls (27). The next report showed that there were no differences between the groups in BPD (28). Furthermore, while BPD was seen in 30 % of infants with PDA who had received placebo, it was significantly more frequent (43 %) in infants who were treated with indomethacin and later still developed PDA. It was suggested that this could be related to early fluid retention caused by indomethacin, a COX inhibitor that affects kidney function. It has previously been shown that premature infants with a relatively greater postnatal weight loss due to reduction of extracellular fluid space have less tendency to develop BPD than infants with less weight loss (2). It was therefore suggested that the increase in BPD after treatment with indomethacin could be attributed to increased extracellular fluid also in the lungs, which would give rise to a need for increased pressure and oxygen during mechanical ventilation.

In the last report from the TIPP study it was found that surgical closure of a PDA reduced mortality to almost a significant extent. However, neurosensory impairment was also significantly increased by 18 months of age, as were retinopathy of prematurity and BPD (29). These findings are also supported by others (30). Furthermore it has been shown that there is a general association between (any) surgery in the neonatal period and neurosensory impairment at five years of age (31), indicating that surgery (and anesthesia) might be independent risk factors in very low birth weight infants.

Conclusions

There seem to be convincing data to conclude that there is no indication for prophylactic or early treatment of a PDA in a small premature infant, even if the infant needs mechanical ventilation because of respiratory distress syndrome. Furthermore, there is no evidence that a haemodynamically significant PDA contributes in any way to later complications and final outcome. A PDA does not impair pulmonary function and does not increase the incidence of BPD. In most cases, a PDA will eventually close spontaneously without treatment. Infants with a PDA who develop heart failure should therefore primarily be treated accordingly, with fluid restriction, diuretics and inotropic drugs. Surgical closure of PDAs should be avoided.

The shift in paradigm with respect to how to treat premature infants with PDA has resulted in increased acknowledgement of the fact that evidence-based data on these matters are largely lacking, even when it comes to infants with a large shunt and failure to sustain cardiac output with reduced or even reversed aortic blood flow (3–5). The last report from the TIPP study might indicate that surgical closure could be of value for the survival of such infants, even though surgery seems to increase neurosensory impairment (28). As pointed out by others (5), this should probably be evaluated in a randomised study of the sickest and smallest infants, comparing surgical closure to placebo (5). Although it could be argued that such a study would be unethical in relation to the well established tradition of active treatment of a significant PDA, it could also be argued that it would be unethical not to conduct such a study (5). In our view, measurement of cardiac output should be an important variable in such a study.

Conflicts of interest given: None

Literature

1. Clyman RI. Mechanisms regulating the ductus arteriosus. Biol Neonate 2006; 89: 330–5.
2. Oh W, Poindexter BB, Perritt R et al. Association between fluid intake and weight loss during the first ten days of life and risk of bronchopulmonary dysplasia in extremely low birth weight infants. J Pediatr 2005; 147: 786–90.
3. Laughon MM, Simmons MA, Bose CL. Patency of the ductus arteriosus in the premature infant: is it pathologic? Should it be treated? Curr Opin Pediatr 2004; 16: 146–51.
4. Bose BL, Laughon MM. Patent ductus arteriosus: lack of evidence for common treatments. Arch Dis Child Fetal Neonatal Ed 2007; 92: F498-F502.
5. Bose CL, Laughon ML. Treatment to prevent patency of the ductus arteriosus: Beneficial or harmful? J Pediatr 2006; 148: 713–4.
6. Clyman RI, Chome N. Patent ductus arteriosus: evidence for and against treatment. J Pediatr 2007; 150: 216–9.
7. Spitzer AR, Davis J, Clarke WT et al. Pulmonary hypertension and persistent fetal circulation in the newborn. Clin Perinatol 1988; 15: 389–413.
8. Mellander M, Larsson LE. Effects of left-to-right ductus shunting on left ventricular output and cerebral blood flow velocity in 3-day-old preterm infants with and without severe lung disease. J Pediatr 1988; 113: 101–9.
9. Perlman JM, Hill A, Volpe JJ. The effect of patent ductus arteriosus on flow velocity in the anterior cerebral arteries: ductal steal in the premature newborn infant. J Pediatr 1981; 99: 767–71.
10. Clyman RI, Mauray F, Heymann MA et al. Cardiovascular effects of patent ductus arteriosus in preterm lambs with respiratory distress. J Pediatr 1987; 111: 579–87.
11. Skelton R, Evans N, Smythe J. A blinded comparison of clinical and echocardiographic evaluation of the preterm infant for patent ductus arteriosus. J Paediatr Child Health 1994; 30: 406–11.
12. Gerhardt T, Bancalari E. Lung compliance in newborns with patent ductus arteriosus before and after surgical ligation. Biol Neonate 1980; 38: 96–105.

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13. Heldt GP, Pesonen ET, Merrit TA et al. Closure of the ductus arteriosus and mechanics of breathing in preterm infants after surfactant replacement therapy. Pediatr Res 1989; 25: 305–21.
14. Stefano JL, Abbasi S, Pearlman SA et al. Closure of the ductus arteriosus with indomethacin in ventilated neonates with respiratory distress syndrome. Am Rev Respir Dis 1991; 143: 236–9.
15. Farstad T, Bratlid D. Pulmonary effects of closure of patent ductus arteriosus in premature infants with severe respiratory distress syndrome. Eur J Pediatr 1994; 153: 903–5.
16. Kluckow M, Evans N. Superior vena cava flow in newborn infants: a novel marker of systemic blood flow. Arch Dis Child Fetal Neonatal Ed 2000; 82: F182-F187.
17. Osborn DA, Evans N, Kluckow M. Effect of early targeted indomethacin on the ductus arteriosus and blood flow to the upper body and brain in the preterm infant. Arch Dis Child Fetal Neonatal Ed 2003; 88: F477-F482.
18. Cooke L, Steer P, Woodgate P. Indomethacin for asymptomatic patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev 2003; no. 2: CD003745.
19. Malviya M, Ohlsson A, Shah S. Surgical versus medical treatment with cyclooxygenase inhibitors for symptomatic patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev 2003; no. 3: CD003951.
20. Ohlsson A, Wakia R, Shah S. Ibuprofen for the treatment of patent ductus arteriousus in preterm and/or low birth weight infants. Cochrane Syst Rev 2005; no. 4: CD003481.
21. Herrera C, Holberton J, Davis P. Prolonged versus short course of indomethacin for the treatment of patent ductus arteriosus in preterm infants. Cochrane Syst Rev 2007; no. 2: CD003480.
22. Cotton RB, Stahlman MT, Kovar I et al. Medical management of small preterm infants with symptomatic patent ductus arteriosus. J Pediatr 1978; 92: 467–73.
23. Markestad T, Kaaresen PI, Rønnestad A et al. Early death, morbidity and need of treatment among extremely premature infants. Pediatrics 2005; 115: 1289–98.
24. Cassady G, Crouse DT, Kiklin JW et al. A randomized controlled trial of very early prophylactic ligation of the ductus arteriosus in babies who weighed 1000 g or less at birth. N Engl J Med 1989; 320: 1511–6.
25. Bandstra ES, Montalvo BM, Goldberg et al. Prohylactic indomethacin for prevention of intraventricular hemorrhage in premature infants. Pediatrics 1988; 82: 533–42.
26. van Bel F, Van de Bor M, Stijnen T et al. Cerebral blood flow velocity changes in preterm infants after a single dose of indomethacin: duration of its effect. Pediatrics 1989; 84: 802–7.
27. Schmidt B, Davis P, Moddemann D et al. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med 2001; 344: 1966–72.
28. Schmidt B, Roberts RS, Fanaroff A et al. Indomethacin prophylaxis, patent ductus arteriosus, and the risk of bronchopulmonary dysplasia: Further analyses from the trial of indomethacin prophylaxis in preterms (TIPP). J Pediatr 2006; 148: 730–4.
29. Kabra NS, Schmidt B, Roberts RS et al. Neurosensory impairment after surgical closure of patent ductus arteriosus in extremely low birth weight infants. Results from the Trial of Indomethacin Prophylaxis in Preterms. J Pediatr 2007; 150: 229–34.
30. Chorne N, Leonard C, Piecuch R, Clyman RI. Patent ductus arteriosus and its treatment as risk factors for neonatal and neurodevelopmental morbidity. Pediatrics 2007; 119: 165–74.
31. Victorian Infant Collaborative Study Group. Surgery and the tiny baby: sensorineural outcome at 5 years of age. J Paediatr Child Health 1996; 32: 167–72.